Associations between the ultrasound features of invasive breast cancer and breast cancer specific survival

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Key words

Prognosis

Breast neoplasms

Ultrasound

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Abbreviations

U/S = Ultrasound

DNST = Ductal carcinomas of no specific type

ROC = Receive operating characteristic

HER-2 = Human epidermal growth factor receptor 2

ER = Estrogen receptor

PR = Progesterone receptor

ILC = Invasive lobular carcinoma

ACR = American College of Radiology

BCSS = Breast cancer specific survival

LVI = Lymphovascular invasion

Introduction

Knowledge of prognostic factors in breast cancer allows treatment options to be refined by identifying which patients may benefit from adjuvant therapies. Increasing use of neoadjuvant therapy means that indicators of prognosis are required prior to surgery. While

receptor status and histological grade estimation are available from diagnostic core needle biopsy, information on definitive grading, sizing and nodal status is not available prior to excision. There is therefore a need for alternative indicators of prognosis, and imaging may be able to provide such information.

Traditionally, breast cancer prognosis is predicted based on tumour size, lymph node status, histological grade and the presence of lymphovascular invasion (LVI) [1]. Other factors, including histologic tumour type [2] and molecular markers, contribute to management and prognostic assessment [3,4].

Given the increasing use of neoadjuvant chemotherapy in breast cancer patients, the availability of prognostic information prior to surgery is essential. Several studies have investigated the prognostic significance of mammographic features, identifying, for example, the excellent prognosis of spiculate masses smaller than 15mm [2], whereas there are conflicting results regarding the prognostic significance of comedo calcification [5,6].

Associations between ultrasound (U/S) findings and features such as histological grade, hormone receptor status and histological and molecular subtypes have also been studied [7]. Thus, there is a positive correlation between tumour size at diagnosis and histological grade, likely due to higher mitotic rates, and high grade tumours tend to have round shapes with indistinct margins [8]. Lamb et al. [9] demonstrated that 36% of high-grade tumours show acoustic enhancement on U/S. Basal phenotype cancers are generally aggressive, high-grade and carry a poor prognosis [4]. These tumours exhibit epithelial-mesenchymal transition and pushing margins [10], features which correlate with lack of an echogenic halo at U/S [11]. Triple-negative cancers have increased likelihood of early recurrence and distant metastases. On U/S, they have oval or round shapes with

circumscribed margins, reflecting their rapidly proliferating nature [12,13]. Calcifications are rare [14] and they are less likely to show posterior acoustic shadowing [15].

However, to the best of our knowledge, there are no studies purely investigating the prognostic significance of U/S features. Therefore, the aim of this study was to identify whether U/S features of breast cancer have prognostic significance, given that they vary with known pathologic prognostic features.

Materials and Methods

Study Design

This retrospective observational study was exempted from ethical approval review by the National Research Ethics Service, who waived the requirement for informed consent. The data was taken from a prospectively collected database, for which ethical approval was unnecessary as it was considered service evaluation by the Ethics committee.

A database of all U/S lesions undergoing biopsy has been kept since April 2010. U/S size and biopsy results are collected prospectively.

A retrospective analysis was undertaken of the U/S features of all invasive cancers entered on the database between April 2010 and April 2012, irrespective of mode of treatment. Inclusion criteria included all U/S visible lesions shown to be invasive breast cancer at histology. Women with recurrent cancer or who had metastatic disease at presentation were excluded.

Assessment was performed by an expert breast radiologist with 25 years of breast imaging experience, who was blinded to outcomes.

Breast U/S was performed using *Supersonic Imaging Aixplorer* ® U/S machine and a 12 MHz linear array probe by consultant radiologists or specialist breast sonographers in the breast unit. The breast probe setting on this ultrasound machine automatically defaults to compounding.

Variables

The U/S features of the lesions were evaluated retrospectively from the recorded images and documented according to the American College of Radiology BI-RADS© lexicon (fifth edition)[16]. Features assessed included tissue composition (homogeneous fatty, homogeneous fibroglandular, mixed), mass shape (oval, round, irregular), orientation (parallel or non-parallel), margins (circumscribed or non-circumscribed), echo pattern (anechoic, hyperechoic, complex cystic-solid, hypoechoic, isoechoic, heterogeneous), posterior effect (none, enhancement, shadowing, combined), calcifications (in a mass, outside a mass, intraductal or none) and associated features (distortion, duct changes, skin changes, focal oedema).

Focal oedema was defined as diffuse subtle increase in echogenicity within the adjacent 10 – 20mm of surrounding fat. Figure 1A illustrates an example of focal oedema. Distal acoustic effect was classified into no posterior effect, posterior acoustic enhancement, posterior acoustic shadowing and combined effect. Figure 1B illustrates a case demonstrating posterior acoustic enhancement. Tissue composition was assigned according to the echotexture of the breast tissue immediately surrounding the breast tumour.

Skin involvement was defined as skin thickening ≥2.5mm at U/S or direct skin invasion. The epidermis and dermis have a normal thickness of 0.5 – 2.0mm on imaging [17]. We considered a skin thickness of 2.5mm at U/S, which is above the normal range for normal

skin thickness, as a cut-off value for skin thickening so that borderline cases would not be included as positives. Changes were further classified as skin thickening only, direct skin invasion or a combination of both features. Figure 2A illustrates the florid lymphovascular plexus located immediately beneath the skin. Figure 2B illustrates a case of skin thickening only overlying a breast tumour. Figure 2C illustrates an example of direct skin invasion by the tumour.

For analysis purposes, tumour size was treated as a continuous variable and analysed using Receiver Operating Characteristic (ROC) curves. For illustrative purposes only, U/S tumour size was divided into three groups; ≤ 10.00mm, > 10.01 – 20.00mm and > 20.00mm.

Patient survival and cause of death were ascertained from local and national computer records. Patient who died with metastatic disease were assumed to have died from metastatic breast cancer.

Statistical Analysis

Statistical analysis of categoric variables was carried out using Kaplan-Meier survival curves. Statistical significance was tested using the Log-Rank test. Survival according to U/S size was assessed using receiver operating characteristic (ROC) curves and by Kaplan-Meier survival curves of grouped data. Multivariate analysis of factors that were significant at univariate analysis was carried out using the Cox Regression analysis.

All statistical analyses were carried out by using MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016) and $p < 0.05$ was taken to indicate a significant difference.

Results

Patient Characteristics and Descriptive Data

Four patients with recurrent breast cancer and 10 patients with metastatic disease at presentation were excluded from the study. Thus, the final study group consisted of a total of 319 consecutive patients with 335 breast cancer lesions, of which 209 (62%) were symptomatic and 126 (38%) had screen-detected cancers. Two patients had bilateral breast cancers and 6 had multifocal lesions (2 lesions) in the same breast. U/S visible lesions detected on second-look U/S following Magnetic Resonance Imaging (MRI) were not included. None of the patients with multifocal lesions or bilateral breast cancers died. Patient age ranged from 36 – 95 years (mean age of 63 years).

There were 30 breast cancer deaths and 45 non-breast cancer deaths in the cohort. The mean follow-up in those alive, at the time of ascertainment, was 80.9 months. Two hundred and seventy-six patients (82.3%) were managed by primary surgery, 29 patients (8.7%) received neoadjuvant chemotherapy, 9 patients (2.7%) received neoadjuvant endocrine therapy and 21 patients (6.3%) were managed with primary endocrine therapy.

Ultrasound and Histological Characteristics

At histology, 36 (10.7%) were grade 1 tumours, 144 (43.0%) were grade 2 and 155 (46.3%) were grade 3 tumours. Table 1 describes the pathological and molecular characteristics of the study sample in relation to the number of breast cancer deaths in each sub-group. Table 2 describes the frequency of U/S features in relation to the number of breast cancer deaths in each sub-group. Twenty-three of the 30 breast cancer deaths (77%) occurred in Grade III tumours. Seventeen of the 30 breast cancer deaths (57%) occurred in

patients who were treated by primary surgery, all of whom had tumours greater than or equal to 15mm in size.

Ultrasound Characteristics and Breast Cancer Specific Survival

At univariate analysis, large U/S tumour size, the presence of skin involvement (skin thickening and/or direct invasion), focal oedema and the presence of distal acoustic enhancement were all associated with poorer breast cancer specific survival (BCSS).

Using ROC analysis, the area under the curve was 0.72. This is depicted in figure 3A, (p = < 0.0001). This is illustrated by the Kaplan Meier survival curve (figure 3B) which shows that patients with an U/S tumour size between 10.01 - 20mm were twice as likely to die from breast cancer, and patients with an U/S tumour size > 20mm were eight times more likely to die from breast cancer as compared to those with an U/S tumour size ≤ 10.00mm.

Distal acoustic enhancement was associated with a 76% 5-year BCSS compared to 88%, 96% and 100% BCSS for those with distal shadowing, no distal effect or combined effect respectively (p = 0.0002) (Figure 4). Twelve breast cancer deaths occurred in the 56 tumours (21%) demonstrating distal acoustic enhancement as compared to a 3% breast cancer death rate in tumours showing no distal acoustic effect, an 8% breast cancer death rate in tumours showing posterior acoustic shadowing and a 0% breast cancer death rate in tumours showing a combined posterior effect.

Skin involvement (skin thickening over the mass and/or direct invasion) was associated with a 73% 5-year BCSS compared to 92% in women without skin involvement (p = < 0.0001) (Figure 5). In fact, 13 breast cancer deaths occurred in the 56 tumours (23%) with skin changes as compared to a 6% breast cancer death rate in tumours without skin involvement.

Although skin involvement was detected by U/S in 56 (16.7%) patients, clinical dermal involvement was documented in only 14 (4.2%) cases (skin oedema = 7, skin ulceration = 3, lesions tethered to the skin = 4), in whom 3 breast cancer deaths occurred. In the 42 cases with non-clinically apparent skin involvement, 10 breast cancer deaths occurred. Therefore, the vast majority of breast cancer deaths in this patient sub-group occurred in patients without clinical skin involvement. When looking at the type of skin involvement (skin thickening only, direct invasion only and combined type), the number of patients in each group was too small for subgroup analysis.

Focal oedema was associated with a 56% 5-year BCSS compared to 89% in women without associated oedema (p = 0.0002) (Figure 6). Four breast cancer deaths occurred in the 12 lesions (33%) that demonstrated focal oedema on U/S as compared to a 6% breast cancer death rate associated with lesions not associated with focal oedema. Six of the cases with focal oedema (50%) also had associated skin thickening.

The overall BI-RADS assessment category was of borderline significance (p = 0.0538) with tumours in category 5 having an 83% 5-year BCSS compared to tumours in category 3 and category 4 having a 100% and a 94% 5-year BCSS respectively. The presence of calcifications within the mass was not significant (p = 0.0918). None of the tumours in the cohort showed U/S evidence of calcifications outside a mass or within the ducts.

Mass shape, echogenicity, margin characteristics, orientation and duct changes on U/S were not significant at univariate analysis.

At multivariate analysis of factors that were significant at univariate analysis, skin involvement, posterior acoustic enhancement and focal oedema maintained prognostic significance. U/S tumour size lost significance. Table 3 depicts the final model of stepwise multivariate analysis for BCSS.

Analysis of sub-groups according to immunophenotype could not be done due to the small number of breast cancer deaths.

Discussion

The established prognostic factors for invasive breast cancer are lymph node stage, histological grade, histological size and LVI. In addition, the presence of specific molecular markers, such as ER and HER2, patient age and mode of presentation provide additional prognostic information. Our underlying hypothesis was that the U/S features of breast cancer have prognostic significance, which can be used to guide the use of neoadjuvant systemic treatment.

Our study demonstrates that skin involvement, posterior acoustic enhancement and focal oedema on U/S are strongly and independently associated with poor breast cancer specific survival in women with invasive breast cancer.

The poor outcome associated with skin involvement at U/S is likely related to the presence of a rich vascular and lymphatic plexus beneath the skin. The presence of LVI is a recognised poor prognostic factor in a wide range of tumour types, including breast cancer and malignant melanoma, both of which exhibit a strong tendency to lymphatic spread [18].

Distant metastases are the cause of most deaths in primary cutaneous melanoma [19]. LVI is considered a sign of aggressive disease that leads to regional lymph node and distant metastasis, with a positive lymphatic invasion status being an unfavourable prognostic factor even in patients without regional lymph node metastases [20–26]. Tas et al. [21] demonstrated that LVI has significant prognostic impact on nodal involvement, recurrence and overall survival in cutaneous melanoma.

Similarly, several studies [27,28] have shown LVI in breast cancer to be an adverse prognostic marker even in patients with node-negative disease.

Therefore, we hypothesise that skin involvement at U/S results in invasion of the cutaneous lymphovascular plexus in a mechanism similar to that of malignant melanoma. This would explain the prognostic significance of both skin involvement and focal oedema at ultrasound. In fact, disease processes that result in breast oedema, such as tumour in the breast dermal lymphatics and congestive heart failure, are typically associated with skin thickening [29,30].

Interestingly, three studies have shown that tumour-to-skin distance is an independent predictor of axillary lymph node metastasis in breast cancer [31–33]. Breast cancers located closer to the skin were found to have a higher incidence of axillary nodal metastasis, even in patients with clinically node-negative early-stage disease. However, none of these studies investigated the association with breast cancer mortality.

Given the strong association between skin involvement and breast cancer mortality in our study, and given the fact that the vast majority of breast cancer deaths in this patient sub-group occurred in patients without clinical skin involvement, the routine reporting of the skin overlying the tumour on breast U/S examinations should be considered.

The association between posterior acoustic enhancement and poor BCSS can be explained by the known relationship between posterior acoustic enhancement and high pathologic grade. In this study, the majority of tumours demonstrating posterior acoustic enhancement were high grade. Lamb et al. [9] showed that high-grade invasive cancers were more likely to demonstrate posterior acoustic enhancement. A further study by Rotstein et al. [34] showed that Grade 3 invasive ductal carcinoma is more likely to cause posterior enhancement or posterior isoechogenicity than posterior shadowing. It has been suggested

that tumours which demonstrate posterior enhancement are more cellular [35,36] and that it is the organisation rather than the absolute amount of fibrous tissue that determines tumour attenuation characteristics [37]. Tumours that demonstrate acoustic enhancement have decreased desmoplasia [36-38]. Therefore, the prognostic significance of this U/S feature was not unexpected.

In this study, U/S size was a significant prognostic factor in univariate but not in multivariate analysis. Tumour size is a time-dependent prognostic factor, which has been shown in many studies to influence outcome [39]. However, its significance is minor once nodal stage and pathologic grade are taken into account.

Survival of breast cancer is obviously dependent on the treatment received, particularly systemic therapy. The type and benefit of systemic therapy are molecular subtype dependent but unfortunately our study is too small to allow such analysis to be performed.

Limitations of this study include the relatively small sample size from a single centre. Images were reviewed by one consultant radiologist, so the question of reproducibility of U/S features has not been addressed. Consistency of reporting of distal effect may be variable, as some lesions had a mixed pattern. Measuring skin thickness was easier and more likely to be highly repeatable. U/S features were documented by retrospective review, even though most data was acquired prospectively, and therefore further image optimisation was not possible. The small percentage of invasive cancers that are not visible on ultrasound are obviously not included in our study. These lesions are, however, usually small and unlikely to lead to breast cancer death. Sub-analysis by molecular subtype would have been interesting, but the small number of breast cancer deaths in each group would have made it impractical.

In conclusion, we have found focal oedema, skin involvement and posterior enhancement on U/S to be strongly associated with BCSS in an unselected breast cancer population. Only 25% of those with U/S detected skin involvement had clinical skin involvement. We hypothesise that skin involvement leads to invasion of the rich subdermal plexus of lymphatics and veins leading to systemic spread. The effect of posterior acoustic enhancement on mortality is most likely due to its association with high-grade tumours.

Compliance with Ethical Standards

The article does not contain any studies with human participants or animals performed by any one of the authors.

This retrospective observational study was exempted from ethical approval review by the National Research Ethics Service, who waived the requirement for informed consent.

Acknowledgements and Disclosures

This study was unfunded.

The authors have nothing to disclose. The authors declare that they have no conflict of interest.

Submission Declaration

The work described has not been published previously and is not under consideration for publication elsewhere. Its publication is approved by all authors. If accepted, it will not be published elsewhere in the same form, in English or any other language, including electronically without the written consent of the copyright-holder.

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Tables and Figures

Group	Numbers	Number of breast cancer deaths (%)
Grade		
1	36	0 (0)
2	144	7 (5)
3	155	23 (15)
ER		
Positive	272	17 (6)
Negative	63	13 (21)
$HER2^{+}$		
Positive	34	2 (5.8)
Negative	297	28 (9)
Invasive size*		
< 15mm	85	0 (0)
≥ 15mm	185	17 (9)
Lymph node status*		
Positive	68	7 (10)

Negative	199	9 (5)
Vascular invasion*		
Positive	67	7 (10)
Negative	202	10 (5)
Histological type		
DNST	212	24 (11)
Lobular	28	3 (11)
Tubular	11	0 (0)
Mucinous	4	1 (25)
Papillary	9	0 (0)
Other	71	2 (3)

Table 1: Pathological and molecular characteristics of our study population.

*Denominators for invasive size, lymph node status and vascular invasion are fewer than 335 due to women receiving neoadjuvant and primary systemic therapy. Size, vascular invasion and nodal positivity is only reported in those undergoing immediate surgical management.

*One patient undergoing immediate operative treatment did not undergo lymph node dissection because of comorbidities.

+HER2 results were not available in 4 cases.

DNST = Ductal carcinoma of no specific type

Feature	Numbers	Number of Breast Cancer

		Deaths (%)
Echo pattern		
Hyperechoic	5	0 (0)
Complex cystic solid	1	0 (0)
Hypoechoic	253	23 (9)
Isoechoic	26	1 (4)
Heterogeneous	50	6 (12)
Posterior acoustic effect		
None	97	3 (3)
Enhancement	56	**12 (21)**
Shadowing	179	15 (8)
Combined	3	0 (0)
Tumour shape		
Oval	31	0 (0)
Round	11	1 (9)
Irregular	284	29 (10)
No mass	9	0 (0)
Tumour orientation		
Non parallel	128	11 (9)
Parallel	198	19 (10)
No mass	9	0 (0)
Surrounding Tissue composition		
Fatty	59	9 (15)

Mixed	233	17 (7)
Glandular	43	4 (9)
Tumor margins		
Circumscribed	41	5 (12)
Non-circumscribed	294	25 (9)
Margins		
Indistinct	285	24 (8)
Distinct	50	6 (12)
Microlobulated margins		
Microlobulation present	216	22 (10)
Microlobulation not present	110	8 (7)
No mass	9	0 (0)
Angular margins		
Yes	177	17 (10)
No	149	13 (9)
No mass	9	0 (0)
Spiculated margins		
Yes	28	2 (7)
No	298	28 (9)
No mass	9	0 (0)
Calcifications in a mass*		
Yes	47	7 (15)

No	279	23 (8)
No mass	9	0 (0)
Associated features – Duct changes		
Duct changes		
No duct changes	65	6 (9)
	270	24 (9)
Associated features – skin changes		
Skin changes	56	13 (23)
Direct invasion	5	1 (20)
Skin thickening	37	11 (30)
Direct invasion + skin thickening	14	1 (7)
No changes	279	17 (6)
Associated features – focal oedema		
Oedema		
No oedema	12	4 (33)
	323	26 (8)

Table 2: Frequency of the ultrasound features in our study population.

*In our study, calcifications were only demonstrated within the mass.

Feature	B	SE	Wald	*P*	Exp(b)	95% CI of Exp(b)

Focal oedema	1.3724	0.5407	6.4434	0.0111	3.9449	1.3671 to 11.3832
Posterior acoustic enhancement	1.1425	0.3810	8.9936	0.0027	3.1346	1.4856 to 6.6140
Skin changes	1.2757	0.3794	11.3046	0.0008	3.5813	1.7024 to 7.5340

Table 3: Final model of stepwise multivariate analysis for Breast Cancer Specific Survival (BCSS). Data are for all cases and include focal oedema, posterior acoustic enhancement and skin changes versus other radiological features.

Exp(b) = The exponential of the b coefficient

SE = Standard error